Remarks

Amendments to original Claims 1, 22, and 23 have been proposed. These amendments are being proposed merely to correct typographical errors appearing in names of the "C_1-C_6 alkyl-aryl" and "C_1-C_6 alkyl-(C_3-C_{10})cycloalkyl" substituents. Basis for these amendments may be found in the specification at page 4 (line 13-18) and page 4 (line 24) through page 5 (line 2).

Claims 26-40 have been proposed for addition to the pending claims. These claims relate to compositions and methods of use drawn specifically to the compounds as claimed in original Claims 9, 11, 13, 15, and 17. Basis for the subject matter of the added claims may be found in the specification at pages 23 (lines 16-25) and page 25 (line 1) through page 26 (line14), as well as the original claims 20, 22, and 23.

As the above amendments are being proposed merely to correct typographical mistakes or to more particularly claim the subject matter of the present invention, Applicant submits that said amendments do not encompass new matter. Applicant courteously requests entry of the presently submitted amendments.

Claims 1-23 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Salhoff *et al.*, *Neuropharm.* 34(9): 1159-1168 (1995), in view of Bundgaard (WO 88/01615). These claims relate to simple alkyl (optionally substituted with a limited number of defined substituents) or alkenyl monoesters of the excitatory amino acid receptor antagonist (3*S*,4a*R*,6*R*,8a*R*)-6-[2-(1(2)*H*-tetrazole-5-yl)ethyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid, as well as therapeutic methods and compositions comprising such monoesters. Applicant respectfully submits that rejection of Claims 1-23 is inappropriate on the ground that the Examiner has failed to establish that the subject matter of the present invention is *prima facie* obvious in view of the cited art.

"The Patent and Trademark Office has the burden of showing a *prima facie* case of obviousness." *In re Bell*, 26 U.S.P.Q.2d 1529, 1530 (Fed. Cir.1993). Furthermore,

> to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all claim limitations.

M.P.E.P. §2143. Further still, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure." *In re Vaeck*, 20 U.S.P.Q.2d. 1438 (Fed. Cir.1991).

Neither Salhoff nor Bundgaard disclose or suggest the compounds of the present claims. Indeed, as acknowledged by the Examiner, "Salhoff does not teach the ester on the three position of the isoquinoline core." (Official Action, dated 02/03/2006, p.3, ln. 2-3). In addition, the Examiner's reliance on Bundgaard in efforts to support the general proposition that it would have been obvious to one of ordinary skill in the art to make "an ester prodrug formulation with a reasonable expectation of getting a prodrug having better capabilities that the parent drug." (Official Action, dated 02/03/2006, p.3, ln. 8-10) is of no benefit. Indeed, a close reading of Bundgaard actually refutes the Examiner's position. First, Bundgaard, when considered as a whole, does not suggest making the simple alkyl or alkenyl esters required by the present claims. Instead, Bundegaard requires esters comprising a highly functionalized alkyl moiety, i.e., an N,N-disubstituted-aminocarbonyl alkyl moiety, attached through the carboxyl residue of the drug. The present claims, however, do not embrace such a highly functionalized substituent. Furthermore, Bundgaard explicitly states

> . . . several aliphatic or aromatic esters of carboxylic acid drugs are not sufficiently labile in vivo to ensure a sufficiently high rate and extent of prodrug conversion. For example simple alkyl and aryl esters of penicillins are not hydrolyzed to active free penicillin acid in vivo . . . and therefore have no therapeutic potential . . . Similarly, the much reduced anti-inflammatory activity observed for the methyl or ethyl esters of naproxen . . . and fenbufen . . . relative to the free acids may be ascribed to the resistance of the esters to be hydrolyzed in vivo. . . . Pentopril is another ethyl ester prodrug of an angiotensin-converting enzyme inhibitor which also is highly stable in human plasma. In this case less than 50% of an oral dose of the prodrug appears to be deesterified to the active parent acid.

WO 88/01615 (page 2, line 18 through page 3, line 9)(citations omitted).

Thus, Bundgaard clearly requires the use of highly functionalized esters to overcome the identified problems with simple carboxylic acid derivatives. Therefore, Bundgaard provides no suggestion or motivation to produce the simple esters contemplated by the present claims. Moreover, even if one would insist on going forward to produce simple esters, in spite of the teachings of Bundgaard that such esters would be ineffective, there could be no expectation of success with respect to such simple esters. Even if there were

motivation to combine the asserted references, the resulting combination would comprise the highly functionalized esters of Bundegaard, not the simple esters contemplated by the present claims. Therefore, the Examiner has failed to establish a *prima facie* case of obviousness.

As discussed above, none of the parameters which must be met to establish a *prima facie* case of obviousness (i.e., suggestion or motivation, reasonable expectation of success, teaching as to all the claim limitations) have been met by the present rejection. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a), and passage of the present case to allowance, are respectfully requested.

Respectfully submitted,

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